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(19)

(54) SUBSTITUTED 2-PHENYLIMINO-THIAZOLINES, A PROCESS FOR THEIR PREPARATION AND THEIR USE AS ECTOPARASITICIDES

(71) We, BAYER AKTIENGESELLSCHAFT, a body corporate organised under the laws of Germany, of Leverkusen, Germany (Fed. Rep.), do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described, in and by the following statement:—

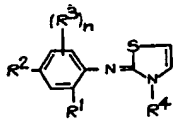
The present invention relates to new substituted 2-phenylimino-thiazolines, a process for their preparation and their use as ectoparasiticides.

It has already been disclosed that 2-phenylimino-thiazoline compounds can be employed as active compounds in agents for combating pests (in this connection see German Auslegeschrift (German Published Specification) 1,218,210 and British Patent Specification 1,027,561).

However, the compounds of the abovementioned patent publications are not active against animal ectoparasites and especially ticks.

In the text of the application, the compound from British Patent Specification 1,027,561 which is structurally closest to the present active compounds according to the invention is compared with active compounds according to the invention, in respect of their tickicidal action.

The present invention provides new substituted 2-phenylimino-thiazolines of the general formula (I)



(I)

in which

R^1 and R^2 can be identical or different and represent optionally substituted alkyl,

R^3 represents optionally substituted alkyl or halogen,

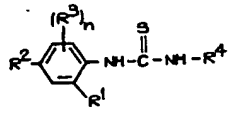
R^4 represents alkyl, cycloalkyl or alkenyl and

n represents 0, 1 or 2,

and their salts.

The compounds of the invention (i.e. the compounds of the formula (I) and their salts) exhibit a powerful ectoparasiticidal action, especially against acarides. Consequently, of the compounds of the invention which are salts, those which are pharmaceutically acceptable are most important and preferred.

Furthermore, it has been found that a compound of the invention is obtained when a substituted phenylthiourea of the formula (II)



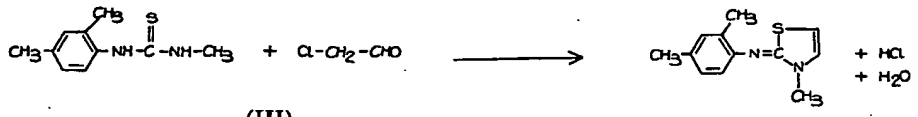
(II)

in which

R^1, R^2, R^3, R^4 and n have the abovementioned meanings, is reacted with a halogenoacetaldehyde or with a compound which splits off a halogenoacetaldehyde, the resulting product being optionally converted to a salt by treatment with an acid.

Surprisingly, the substituted 2-phenylimino-thiazolines according to the invention display a very pronounced ectoparasiticidal action, in contrast to the structurally closely related thiazoline compounds from U.K. Patent Specification 1,027,561.

If N-(2,4-dimethyl-phenyl)-N'-methyl-thiourea and chloroacetaldehyde are used as the starting materials, the course of the reaction can be represented by the following equation:



(III) (IV)

The hydrohalogen acid which is formed during the reaction may be bound by a base (for example with NaOH).

In the formula (I), preferred optionally-substituted alkyl groups for the radicals R^1, R^2 and R^3, are optionally substituted straight-chain or branched alkyl groups with preferably 1 to 6 and especially 1 to 4 carbon atoms. Optionally substituted methyl, ethyl, n- and i-propyl and n-, i- and t-butyl may be mentioned by way of example.

Preferred alkyl groups for the radical R^4 are straight-chain or branched alkyl groups with 1 to 6 and especially 1 to 4 carbon atoms. Optionally substituted methyl, ethyl, n- and i-propyl and n-, i- and t-butyl may be mentioned by way of example.

Preferred alkenyl groups for the radical R^4 are straight-chain or branched alkenyl groups with preferably 2 to 6 and especially 2 to 4 carbon atoms. Vinyl, allyl, crotyl, methallyl, β,β-dimethylvinyl and but-3-en-1-yl may be mentioned by way of example.

As halogen, R^3 in the general formula (I) generally represents fluorine, chlorine, bromine and iodine, preferably chlorine and bromine.

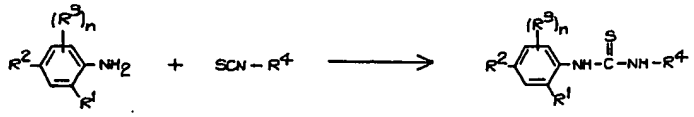
Preferred cycloalkyl groups for the radical R^4 are mono-, bi- and tri-cyclic cycloalkyl groups with 3 to 10 and especially 3, 5 or 6, carbon atoms. Cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl, bicyclo-[2.2.2]octyl and adamantyl may be mentioned by way of example.

The alkyl radicals R^1, R^2 and R^3 in the formula (I) can carry one or more, preferably 1 to 3, especially 1 or 2, identical or different substituents. Substituents which may be mentioned by way of example are: alkoxy with preferably 1 to 4 and especially 1 or 2 carbon atoms, such as methoxy, ethoxy, n- and i-propoxy and n-, i- and t-butoxy, and alkylthio with preferably 1 to 4 and especially 1 or 2 carbon atoms, such as methylthio, ethylthio, n- and i-propylthio and n-, i- and t-butylthio.

The substituted phenylthioureas of the general formula (II) which are used as starting compounds are known and can be prepared in a simple manner according to known methods, either by reacting a substituted phenyl isothiocyanate of the general formula (V) with an aliphatic amine of the general formula (VI):

(V) (VI) (II)

or by reacting a substituted phenylamine of the general formula (VII) with an alkyl isothiocyanate or alkenyl isothiocyanate of the general formula (VIII):



(VII) (VIII) (II)

The radicals R^1, R^2, R^3, R^4 and n in the general formulae (V), (VI), (VII) and (VIII) have the abovementioned meanings.

The halogenoacetaldehydes and the compounds which split off a halogenoacetaldehyde, which are employed according to the invention, are already known.

Examples which may be mentioned of the substituted phenylthioureas of the formula (II), which, according to the process of the invention, may be employed as starting materials, are: N - (2,4 - dimethyl - phenyl) - N' - methyl - thiourea, N - (2,4 - dimethyl - phenyl) - N' - ethyl - thiourea, N - (2,4 - dimethyl - phenyl)- N' - propyl - thiourea, N - (2,4 - dimethyl - phenyl) - N' - isopropyl - thiourea, N - (2,4 - dimethyl - phenyl) - N' - allyl - thiourea, N - (2,4 - dimethyl - phenyl)- N' - methallyl - thiourea, N - (2,4 - dimethyl - phenyl) - N' - crotyl - thiourea, N - (2,4 - dimethyl - phenyl) - N' - cyclopropyl - thiourea, N - (2,4 - dimethyl- phenyl) - N' - butyl - thiourea, N - (2,4 - dimethyl - phenyl) - N' - tert. - butyl- thiourea, N - (2 - methyl - 4 - ethyl - phenyl) - N' - methyl - thiourea, N - (2- methyl - 4 - ethyl - phenyl) - N' - ethyl - thiourea, N - (2 - methyl - 4 - ethyl- phenyl) - N' - allyl - thiourea, N - (2 - ethyl - 4 - methyl - phenyl) - N' - methyl- thiourea, N - (2 - ethyl - 4 - methyl - phenyl) - N' - ethyl - thiourea, N - (2,4- diethyl - phenyl) - N' - methyl - thiourea, N - (2,4 - diethyl - phenyl) - N' - ethyl- thiourea, N - (2,4,5 - trimethyl - phenyl) - N' - methyl - thiourea, N - (2,4,5- trimethyl - phenyl) - N' - ethyl - thiourea, N - (2,4,5 - trimethyl - phenyl) - N'- allyl - thiourea, N - (2,4,5 - trimethyl - phenyl) - N' - cyclopropyl - thiourea, N - (2,3,4 - trimethyl - phenyl) - N' - methyl - thiourea, N - (2,3,4 - trimethyl- phenyl) - N' - ethyl - thiourea, N - (2,3,4 - trimethyl - phenyl) - N' - methallyl- thiourea, N - (2,4,6 - trimethyl - phenyl) - N' - methyl - thiourea, N - (3 - methyl- 2,4 - diethyl - phenyl) - N' - methyl - thiourea, N - (5 - methyl - 2,4 - diethyl- phenyl) - N' - methyl - thiourea, N - (5 - chloro - 2,4 - dimethyl - phenyl) - N'- methyl - thiourea and N - (2,3,4,5 - tetramethyl - phenyl) - N' - methyl - thiourea.

Examples which may be mentioned of the halogenoacetaldehydes, or of compounds which split off a halogenoacetaldehyde, which, according to the process of the invention, may be employed as starting materials, are: chloroacetaldehyde, bromoacetaldehyde, chloroacetaldehyde dimethyl acetal, bromoacetaldehyde diethyl acetal, methyl - (1,2 - dichloroethyl) - ether, ethyl - (1,2 - dichloroethyl)- ether and 2 - chloromethyl - 1,3 - dioxolane.

Examples which may be mentioned of the starting compounds of the formula (VII), which may be employed for the preparation of the compounds of the formula (II), are: 2,4 - dimethylaniline, 2 - methyl - 4 - ethyl - aniline, 2 - methyl - 4 - propyl - aniline, 2 - methyl - 4 - butyl - aniline, 2 - methyl - 4- isopropyl - aniline, 2 - methyl - 4 - isobutyl - aniline, 2 - methyl - 4 - sec. - butyl- aniline, 2 - methyl - 4 - tert. - butyl - aniline, 2 - ethyl - 4 - methyl - aniline, 2,4 - diethylaniline, 2 - ethyl - 4 - isopropylaniline, 2 - ethyl - 4 - tert. - butyl- aniline, 2,4 - diisopropyl - aniline, 2,4 - di - sec. - butyl - aniline, 2,4 - di - tert.- butyl - aniline, 2,4,5 - trimethyl - aniline, 2,3,4 - trimethyl - aniline, 2,4,6 - trimethyl- aniline, 3 - methyl - 2,4 - diethyl - aniline, 5 - methyl - 2,4 - diethyl - aniline, 5 - chloro - 2,4 - dimethylaniline, 5 - bromo - 2,4 - dimethyl - aniline, 5 - fluoro- 2,4 - dimethyl - aniline, 2,5 - dimethyl - 4 - chloro - aniline, 2,3,4,5 - tetra- methyl - aniline, 2 - ethyl - 3,4 - dimethyl - aniline, 2 - methyl - 4 - methoxy- methyl - aniline, 4 - methyl - 2 - methoxymethyl - aniline and 4 - methyl - 2- methylthiomethyl - aniline.

Examples which may be mentioned of alkylamines and alkenylamines of the general formula (VI) are: methylamine, ethylamine, propylamine, isopropyl- amine, butylamine, sec.-butylamine, isobutylamine, tert.-butylamine, allylamine, methallylamine, crotylamine and cyclopropylamine.

The preparation of the isothiocyanates of the formulae (V) and (VIII) from the arylamines of the formula (VII) and the alkylamines of the formula (VI) respectively can be carried out according to known methods, for example by reacting an arylamine of the formula (VII) with thiophosgene or by reacting an N- aryl- or N-alkyl-dithiocarboxylic acid salt with phosgene or an oxidising agent

according to the instructions in Houben-Weyl 'Methoden der Organischen Chemie' ('Methods of Organic Chemistry'), Volume IX, pages 867 to 878. The reaction of an isothiocyanate of the formulae (V) and (VIII) with an amine of the formulae (VI) and (VII) respectively to give a thiourea of the formula (II) can be effected by heating in an inert solvent or in the melt, with or without the addition of a basic catalyst, such as triethylamine (see Houben-Weyl 'Methoden der Organischen Chemie' ('Methods of Organic Chemistry'), Volume IX, pages 889 to 891).

According to the invention, the substituted phenylthiourea of the general formula (II) is reacted with a halogenoacetaldehyde, to give an active compound of the general formula (I).

The reaction of the substituted phenylthiourea of the formula (II) with a halogenoacetaldehyde or with a compound which splits off a halogenoacetaldehyde is preferably carried out in a solvent with the addition of an acid-binding agent.

Examples of solvents which can be used are: alcohols, such as methanol, ethanol and butanol, ketones, such as acetone, butanone and methyl isopropyl ketone, ethers, such as 1,2-dimethoxy-ethane, diisopropyl ether, tetrahydrofurane and dioxane, carboxylic acid derivatives, such as acetonitrile, ethyl acetate and dimethylformamide, aromatic compounds, such as benzene, toluene, xylene and chlorobenzene, aliphatic and cycloaliphatic compounds, such as benzines and ligroins with boiling ranges between 60° and 180°C and cyclohexane, and chlorinated aliphatic compounds, such as methylene chloride, chloroform, carbon tetrachloride and 1,2-dichloroethane.

Examples of acid-binding agents which can be used are: inorganic bases, such as sodium bicarbonate, sodium carbonate, potassium carbonate, tri-sodium phosphate, sodium hydroxide and potassium hydroxide, or organic bases, such as, for example, triethylamine or benzyl-dimethylamine.

Equimolar or approximately equimolar amounts of the two components are used for the reaction of the substituted phenylthiourea of the formula (II) with the halogenoacetaldehyde or with the compound which splits off a halogeno-acetaldehyde and, in particular, it can be appropriate to employ a slight excess (1 to 15 mol %) of the halogenoacetaldehyde or the compound which splits off a halogenoacetaldehyde. For this purpose, the substituted phenylthiourea of the formula (II) is dissolved or suspended in a solvent and the halogeno-acetaldehyde or the compound which splits off a halogenoacetaldehyde is added slowly. The acid-binding agent can also be initially introduced at the same time or can be added only subsequently. The reaction is suitably carried out at temperatures from 0°C up to the boiling point of the solvent used, for example 150°C; the preferred temperature range is from 20°C to 80°C.

Working up of the batches is appropriately carried out by mixing the batch with water in order to remove the salts, extracting the reaction product with a solvent which is immiscible with water, and crystallising or distilling. If the melting point of the reaction product is sufficiently high, the aqueous suspensions can be worked up direct by filtration and drying.

If the condensation reaction is carried out without the addition of an acid-binding agent, it is then also possible to isolate the 2-arylimino-3-alkyl-thiazolines in the form of their salts, for example the hydrochlorides. On the other hand, 2-arylimino-3-alkyl-thiazolines isolated in the form of the bases can also subsequently be converted into their salts by reaction with inorganic or organic acids, for example into the hydrochlorides, hydrobromides, sulphates, phosphates, formates, oxalates, succinates, trifluoroacetates, benzene-sulphonates or naphthalene-1,5-disulphates.

The following may be mentioned as examples of the 2 - arylimino - 3-alkyl - thiazolines of the general formula (I) which can be prepared according to the invention: 2 - (2,4 - dimethyl - phenylimino) - 3 - methyl - thiazoline, 2-(2,4,5 - trimethyl - phenylimino) - 3 - methyl - thiazoline, 2 - (2,4 - diethyl-phenylimino) - 3 - methyl - thiazoline, 2 - (2,4 - dimethyl - phenylimino) - 3-ethyl - thiazoline, 2 - (2,4 - dimethyl - phenylimino) - 3 - propyl - thiazoline, 2 - (2,4 - dimethyl - phenylimino) - 3 - isopropyl - thiazoline, 2 - (2,4 - dimethyl-phenylimino) - 3 - butyl - thiazoline, 2 - (2,4 - dimethyl - phenylimino) - 3-isobutyl - thiazoline, 2 - (2,4 - dimethyl - phenylimino) - 3 - tert. - butyl-thiazoline, 2 - (2,4 - dimethyl - phenylimino) - 3 - allyl - thiazoline, 2 - (2,4-dimethyl - phenylimino) - 3 - methallyl - thiazoline, 2 - (2,4 - dimethyl - phenyl-imino) - 3 - crotyl - thiazoline, 2 - (2,4 - dimethyl - phenylimino) - 3 - (ββ-

dimethyl - vinyl) - thiazoline, 2 - (2 - ethyl - 4 - methyl - phenylimino) - 3-methyl - thiazoline, 2 - (2 - methyl - 4 - ethyl - phenylimino) - 3 - methyl-thiazoline, 2 - (2,4 - di - methyl - 5 - chloro - phenylimino) - 3 - methyl - thiazoline, 2 - (2,3,4 - trimethyl - phenylimino) - 3 - methyl - thiazoline, 2 - (2,3,4,5 - tetramethyl - phenylimino) - 3 - methyl - thiazoline, 2 - (2,4,6 - trimethyl-phenylimino) - 3 - thiazoline, 2 - (2 - methyl - 4 - isopropyl - phenylimino) - 3-methyl - thiazoline, 2 - (2 - tert. - butyl - 4 - methyl - phenylimino) - 3 - methyl-thiazoline, 2 - (2,4 - di - isopropyl - phenylimino) - 3 - methyl - thiazoline, 2-(2,4 - diethyl - phenylimino) - 3 - allyl - thiazoline, 2 - (4 - methyl - 2 - methoxy-methyl - phenylimino) - 3 - methyl - thiazoline and 2 - (4 - methyl - 2 - methyl-thiomethyl - phenylimino) - 3 - methyl - thiazoline.

The active compounds of the general formula (I) and their salts exhibit a powerful pesticidal action, especially against acarides, which, as animal ectoparasites, infest domesticated animals such as cattle, sheep and rabbits. At the same time, the 2-arylimino-3-alkylthiazolines have only a low toxicity to warm-blooded animals. They are therefore very suitable for combating animal ectoparasites of the class of the acarides. In addition, however, they also possess an action against insects.

Examples which may be mentioned are: lice and diptera as well as the larvae thereof.

Economically important ectoparasites, which play a large role especially in tropical and subtropical countries, which may be mentioned are: the Australian and South American cattle tick *Boophilus microplus* and the South African cattle tick *Boophilus decoloratus,* which are both of the family of Ixodidae.

In the course of time ticks, in particular, have become resistant to the phosphoric acid esters and carbonates hitherto used as combating agents, so that the success in combating them is becoming increasingly dubious in many fields. In order to ensure economic livestock-keeping in the infested regions, there is an urgent need for agents with which it is possible reliably to combat all stages of development, that is to say larvae, nymphs, metanymphs and adults, even of resistant strains, for example of the genus *Boophilus.* Strains highly resistant to the phosphoric acid ester agents used hitherto are, for example, the Mackay strain, the Biarra strain and the Mt-Alford strain of *Boophilus microplus* in Australia, and the Berlin-strain of Boophilus decoloratus in South Africa.

The active compounds according to the invention have an equally good action both against strains or normal sensitivity and against resistant strains, for example of *Boophilus.* On customary administration to the host animal they have a direct action on all the parasitic forms on the animal and also have a strong ovicidal action on the adult forms, so that the reproductive cycle of the ticks is interrupted both in the parasitic phase on the animal and also in the non-parasitic phase. Oviposition is prevented and development and hatching is inhibited. In particular, the rapidly occurring excitation effect on all the parasitic forms, which detach wander around on the host animal in an unphysiological manner, drop off and finally die (detaching effect), and especially also the good action against the metanymph stages which, as is known from experience, are difficult to combat, are to be singled out.

Furthermore, the active compounds act in the same way on all the stages of development of multihost ticks, such as, for example, Amblyomma spp. Hyalomma spp, Rhipicephalus spp. Ixodes spp., Haemaphysalis spp. and Dermacentor spp.

A detaching effect is also found with insects, for example lice, such as Haematopinus spp. and diptera, such as Melophagus ovinus.

The active compounds according to the present invention can be converted into the usual formulations, such as solutions, emulsions, suspensions, powders, pastes and granulates. These may be produced in known manner, for example by mixing the active compounds with extenders, that is, liquid or solid or liquefied gaseous diluents or carriers, optionally with the use of surface-active agents, that is, emulsifying agents and/or dispersing agents, and/or foam-forming agents. In the case of the use of water as an extender, organic solvents can, for example, also be used as auxiliary solvents.

The invention specifically provides a formulation for use in the treatment of ectoparasites which comprises a compound according to the invention in admixture with a solid or liquefied gaseous diluent or in admixture with a liquid diluent other than a solvent of molecular weight less than 200 (preferably less than 300) except in the presence of a surface active agent.

As liquid diluents or carriers, there are preferably used aromatic hydrocarbons, such as xylenes, toluene, benzene or alkyl anphthalenes, chlorinated aromatic or aliphatic hydrocarbons, such as chlorobenzenes, chloroethylenes or methylene chloride, aliphatic hydrocarbons, such as cyclohexane or paraffins, for example mineral oil fractions, alcohols, such as butanol or glycol as well as their ethers and esters, ketones, such as acetone, methyl ethyl ketone, methyl isobutyl ketone or cyclohexanone, or strongly polar solvents, such as dimethyl formamide, dimethyl sulphoxide or acetonitrile, as well as water.

By liquefied gaseous diluents or carriers are meant liquids which would be gaseous at normal temperatures and pressures, for example, aerosol propellants, such as halogenated hydrocarbons, for example freon.

As solid diluents or carriers, there are preferably used ground natural minerals, such as kaolins, clays, talc, chalk, quartz, attapulgite, montmorillonite or diatomaceous earth, or ground synthetic minerals, such as highly-dispersed silicic acid, alumina or silicates.

Preferred examples of emulsifying and foam-forming agents include non-ionic and anionic emulsifiers, such as polyoxyethylene-fatty acid esters, polyoxyethylene-fatty alcohol ethers, for example alkylarylpolyglycol ethers, alkyl sulphonates, alkyl sulphates and aryl sulphonates as well as albumin hydrolyzation products; and preferred examples of dispersing agents include lignin sulphite waste liquors and methyl cellulose.

The formulations generally contain between 0.1 and 95% by weight of active compound, preferably between 0.5 and 90% by weight. The use concentrations are prepared from the formulations (see above) by dilution with water. Depending on the use form, they can be varied within a large range and are between 10 and 50,000 ppm (g/g), preferably between 50 and 500 ppm.

Application is carried out in the customary manner, for example by spraying, pour on, spot on, atomising or as a bath (dip).

Other auxiliaries or active compounds, such as disinfectants or particularly suitable insecticides, can also be admixed with the formulations or the ready-to-use solutions.

The invention further provides a method of combating acarides which comprises applying to the acarides, or a habitat thereof, a compound of the invention alone or in admixture with a diluent.

More specifically the invention provides a method of combating ectoparasites on warm-blooded animals which comprises applying to the external surface of the animal, a compound of the invention alone or in admixture with a diluent.

Under the conditions existing in practice, the aqueous solutions and emulsions of the active compounds according to the invention possess good stability, so that the ready-to-use application forms remain active even on prolonged standing and in a pH range of 7—9 for three months and more.

Tick test

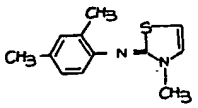
Solvent: 35 parts by weight of ethylene glycol monomethyl ether
35 parts by weight of nonylphenol polycol ether

In order to prepare a suitable formulation, three parts by weight of active compound are mixed with seven parts of the solvent/emulsifier mixture indicated above and the emulsion concentrate thus obtained is diluted with water to the particular desired concentration.

Adult, fully engorged female ticks of the species *Boophilus microplus* (sensitive and resistant) are dipped into these preparations of active compounds for one minute. After dipping 10 female specimens of each of the various tick strains, the ticks are transferred into Petri dishes, the base of which is covered with a filter disc of appropriate size.

After 10 days the activity of the preparation of active compound is determined by ascertaining the inhibition of oviposition, compared with that of untreated control ticks. The active is quoted in per cent, 100% denoting that no further eggs have been deposited and 0% denoting that the ticks have deposited a normal number of eggs.

The active compound investigated, the concentration tested, the parasites tested and the results obtained can be seen from the Table which follows.

Compound	Concentration of the active compound in ppm	Action on *Boophilus microplus* (Biarra strain) in %
2-(3'4-di Methyl-phenyl)-imino-3 methyl-thiazolidine	10,000	0
	1,000	0
known from British Patent 1,027,561	100	0
	10,000	100
	3,000	100
	1,000	100
	300	100
	100	100
	30	100
	10	100
	3	>50
	1	<50
Compound according to the invention	0.3	0

Example.

In vivo tick test on *Boophilus microplus*

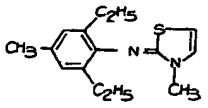
3 parts of active compound are mixed with 7 parts of a mixture consisting of equal parts by weight of ethylene glycol monomethyl ether and nonylphenyl polyglycol ether. The emulsion concentrate thus obtained is diluted with water to the particular desired use concentration.

Cattle which have been infected serveral times (infected 12 times at intervals of 2 days) with resistant tick larvae of the species *Boophilus microplus*, Biarra strain, are sprayed with the preparation of active compound thus obtained.

The action of the preparation of active compound is determined by counting the number of adult female ticks which develop on the treated cattle. This number is compared with the number of adult female ticks which develop on untreated cattle. A compound is the more effective, the fewer the female ticks which develop after the treatment.

The number of adult females which develop on treated and untreated animals in the last three days prior to the time of treatment is used as a criterion of the severity of infestation before treatment.

Activity of the compound, according to the invention, of the formula



at various concentrations against *Boophilus microplus* (Biarra strain) using the pour-on method. All the stages of development are in vivo (cattle).

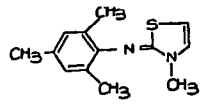
Concentration of the active compound in mg/kg	Days before to treatment −2 – ±0	Number of ticks which lay fertile eggs: Days after treatment +1–3	4–6	7–9	10–12	13–15	16–18	19–21	∈+1–21	Action in %
10	342	0	0	0	0	0	0	0	0	100
	2004	2414	2377	1716	126	363	133	101	7255	–

Adults — Nymphs — Larvae

Metanymphs — Metalarvae

→ Approximate stage of development at the time of treatment →

Activity of the compound, according to the invention of the formula



in various concentrations against *Boophilus microplus* (Biarra strain) when sprayed on by hand. (All the stages of development are in vivo (cattle)).

Concentration of the active compound in ppm	Days before to treatment −2 – ±0	Number of ticks which lay fertile eggs								Action in %
		Days after treatment								
		+1–3	4–6	7–9	10–12	13–15	16–18	19–21	+1–+21	
500	1361	0	0	0	0	0	0	0	0	100
250	1140	0	0	0	0	0	0	0	0	100
125	414	2	0	0	0	0	0	0	0	99.96
Control	2004	2414	2377	1716	126	363	133	101	7230	–

Adults — Nymphs — Larvae

Metanymphs — Metalarvae

→ Approximate stage of development at the time of treatment →

Action of the compound of Example 3, according to the invention, when sprayed by hand on to *Boophilus microplus* (Biarra strain).
All the stages of development are in vivo (cattle).

Concentration of the active compound in ppm	Days before to treatment −2 – ±0	Number of ticks which lay fertile eggs								Action in %
		Days after treatment								
		+1–3	4–6	7–9	10–12	13–15	16–18	19–21	+1–+21	
250	1079	5	0	0	0	0	0	0	5	99.9
Control	1856	1461	862	1008	478	92	42	29	3972	–

Adults — Nymphs — Larvae

Metanymphs — Metalarvae

→ Approximate stage of development at the time of treatment →

Action of the compound of Example 4, according to the invention, when sprayed by hand on to *Boophilus microplus* (Biarra strain).
All the stages of development are in vivo (cattle).

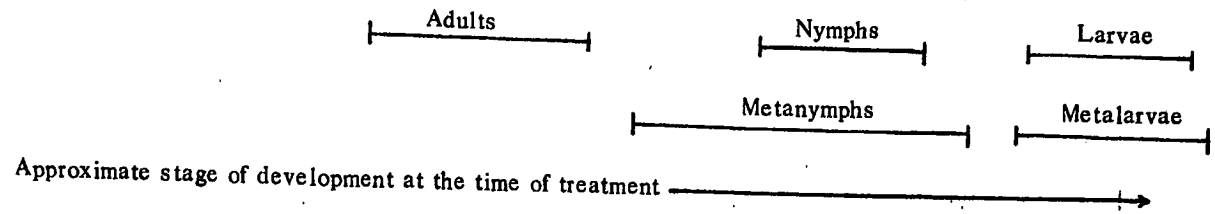
Concentration of the active compound in ppm	Days before to treatment −2 — ±0	Number of ticks which lay fertile eggs								Action in %
		Days after treatment								
		+1–3	4–6	7–9	10–12	13–15	16–18	19–21	ϵ+1–+21	
1000	40	0	0	0	0	0	0	0	0	100
Control	1401	1040	829	1106	477	405	204	50	4111	–

Adults
Nymphs
Larvae
Metanymphs
Metalarvae

Approximate stage of development at the time of treatment →

Action of the compound of Example 5, according to the invention, when sprayed by hand on to *Boophilus microplus* (Biarra strain).
All the stages of development are in vivo (cattle).

Concentration of the active compound in ppm	Days before to treatment −2 – ±0	Number of ticks which lay fertile eggs								Action in %
		Days after treatment								
		+1–3	4–6	7–9	10–12	13–15	16–18	19–21	+1–21	
250	1070	43	9	13	63	22	7	0	157	94
Control	1401	1040	829	1106	477	405	204	50	4111	–



Example 1.

2-(2,4-Dimethyl-phenyl)-imino-3-methyl-thiazoline

100 g of N-(2,4-dimethyl-phenyl)-N'-methyl-thiourea were suspended in 400 ml of acetone and 90 g of a 45% strength aqueous solution of chloroacetaldehyde were added dropwise at 10°C to 15°C. Thereafter the batch was heated to the reflux temperature for 2 hours and the acetone was then largely distilled off. The residue was stirred with 1.5 litres of water and 50 ml of 45% strength sodium hydroxide solution and the oily reaction product was taken up in methylene chloride, dried over potassium carbonate and fractionated: boiling point 145—150°C/0.5 mm Hg, yield: 96 g; 86% of theory. The compound crystallised on seeding or prolonged standing. Fp: 42—43°C.

N-(2,4-Dimethyl-phenyl)-N'-methyl-thiourea, which was used as the starting compound, was prepared in the following manner:

200 g of 4-amino-1,3-dimethylbenzene were dissolved in 200 ml of dioxane and 100 ml of triethylamine, and 124 g of methyl isothiocyanate were added to the solution. When the exothermic reaction had ended and the test for the amine by the diazotisation reaction was negative, the mixture was diluted with 1 litre of warm water and 500 ml of acetic acid and the reaction product was filtered off and washed with water and methanol.

Yield: 282 g: 90% of theory; melting point: 150—152°C.

Example 2.

2-(2,4-Dimethyl-phenyl)-imino-3-methyl-thiazoline

150 g of N-(2,4-dimethyl-phenyl)-N'-methyl-thiourea were dissolved in 800 ml

of acetone and 200 g of finely powdered potassium carbonate and 60 ml of water were added. 117 g of methyl-1,2-dichloroethyl ether (94% strength) were then added dropwise at 10—15°C. Thereafter, the batch was stirred for a further 1 hour at 50°C, the salts were then filtered off and the acetone filtrate was stirred with 4 litres of water and 100 ml of 45% strength sodium hydroxide solution. The oil which had separated out was taken up in methylene chloride, the methylene chloride phase was washed several times with water and dried over potassium carbonate and the methylene chloride was distilled off. This gave 150 g of an oily reaction product which was stirred with 500 ml of petroleum ether at −10°C and was made to crystallise by seeding. The product was filtered off, washed with pre-cooled petroleum ether (boiling point 40—60°C) and dried in vacuo. Yield: 130 g; 76% of theory. Melting point: 42—43°C. According to gas chromatographic analysis, the compound prepared in this way was 98.5% pure.

The NMR and IR spectra and the elementary analysis were compatible with the assumed structure.

Example 3.

2-(2,4,5-Trimethyl-phenyl)-imino-3-methyl-thiazoline

30 g of N-(2,4,5-trimethyl-phenyl)-N'-methyl-thiourea were dissolved in 250 ml of acetone, and 40 g of potassium carbonate and 20 ml of water were added. 22 g of methyl-1,2-dichloroethyl ether (92% strength) were then added dropwise at 10°C. The mixture was stirred for 2 hours at 50° and was then poured into 2 litres of water and 50 ml of 45% strength sodium hydroxide solution. The oily reaction product which had precipitated was taken up in methylene chloride and the extract was washed several times with water, dried over potassium carbonate and fractionated: boiling point: 163—168°C/0.7 mm Hg, yield: 27 g; 81% of theory.

The compound crystallised on standing.

The thiourea which was used as the starting material was prepared as follows:

180 g of 5-amino-1,2,4-trimethylbenzene were dissolved in 200 ml of methylene chloride and added dropwise, at 15—20°C, to a mixture consisting of 208 g of thiophosgene, 600 ml of methylene chloride, 500 ml of water and 180 g of calcium carbonate. The mixture was then warmed under reflux until the evolution of carbon dioxide had ended. The mixture was then filtered and the methylene chloride phase was separated off, dried over potassium carbonate and fractionated: boiling point: 132—136°C/5.0 mm Hg, yield: 203 g of 2,4,5-trimethyl-phenyl isothiocyanate.

100 g of 2,4,5-trimethyl-phenyl isothiocyanate were introduced, at 10°C, into a solution of 47 g of methylamine in 400 ml of methanol. The mixture was stirred for 12 hours at 20° and was warmed under reflux for a further 1 hour. The batch was then diluted with 1 litre of water and the reaction product was filtered off, washed and dried. Yield: 130 g (85% of theory) of N-(2,4,5-trimethyl-phenyl)-N'-methyl-thiourea, melting point: 181—182°C.

Alternatively, the same compound can also be prepared according to the following process:

150 g of 5-amino-1,2,4-trimethyl-benzene are dissolved in 100 ml of dioxane and 150 ml of triethylamine and subsequently 84 g of methyl isothiocyanate are added. The reaction proceeds exothermically and the mixture is allowed to come up to the reflux temperature. As soon as the amine can no longer be detected by the diazotisation reaction, the batch is diluted with 1 litre of wash benzine (boiling point: 60—80°C) and cooled to 20°C and the reaction product is filtered off: Yield: 217 g (94% of theory) of N-(2,4,5-trimethylphenyl)-N'-methylthiourea, melting point: 179—181°C.

Example 4.

2-(2,4-Diethyl-phenyl)-imino-3-methyl-thiazoline

30 g of N-(2,4-diethyl-phenyl)-N'-methyl-thiourea were stirred in 250 ml of acetone and 27 g of chloroacetaldehyde (45% strength aqueous solution) were added dropwise. The mixture was then heated under reflux for 2 hours and subsequently the acetone was distilled off. The residue was stirred with 250 ml of methylene chloride and 60 ml of 20% strength sodium hydroxide solution and the methylene chloride layer was separated off, washed with twice 200 ml of water, dried over potassium carbonate and fractionated.

Boiling point: 149—153°C/0.4 mm Hg; yield; 25.0 g; 75% of theory. The distillate solidified on standing.

The thiourea which was used as the starting material was prepared, as

indicated in Example 3, from 2,4-diethylaniline and methyl isothiocyanate; melting point: 132—134°C.

Example 5.

2-(2,4-Dimethyl-phenyl)-imino-3-ethyl-thiazoline

30.0 g of N-(2,4-dimethyl-phenyl)-N'-ethyl-thiourea are stirred with 250 ml of acetone and 27.0 g of chloroacetaldehyde (45% strength aqueous solution) were added slowly. Thereafter, the mixture was heated under reflux for 2 hours and subsequently the acetone was largely distilled off. The residue was stirred with 250 ml of methylene chloride and 60 ml of 20% strength sodium hydroxide solution and the methylene chloride layer was separated off, washed with water, dried over potassium carbonate and fractionated. Boiling point: 147—152°C/0.8 mm Hg; yield: 25.0 g; 75% of theory.

Example 6.

The following thiazoline derivatives were prepared analogously to Example 5: 2 - (2,4 - dimethyl - phenylimino) - 3 - propyl - thiazoline, boiling point: 155—162°C/0.5 mm Hg; 2 - (2,4 - dimethyl - phenylimino) - 3 - allyl - thiazoline, boiling point: 153—156°C/0.6 mm Hg; 2 - (2 - methyl - 4 - ethyl - phenylimino)-3 - methyl - thiazoline, boiling point: 146—150°C/0.4 mm Hg and 2 - (2,4,5-trimethyl - phenylimino) - 3 - ethyl - thiazoline, boiling point: 165—173°C/0.9 mm Hg.

The N - aryl - N' - alkylthioureas required as starting materials can be prepared according to the processes described in Example 1 and 3; they are the following compounds; N - (2,4 - dimethyl - phenyl) - N' - ethyl - thiourea, melting point: 77—79°C; N - (2,4 - dimethyl - phenyl) - N' - propyl - thiourea, melting point: 66—68°C; N - (2,4 - dimethyl - phenyl) - N' - allyl - thiourea, melting point: 58—60°C; N - (2 - methyl - 4 - ethyl - phenyl) - N' - methyl-thiourea, melting point: 127—128°C and N - (2,4,5 - trimethyl - phenyl) - N' - ethyl-thiourea, melting point: 133—135°C.

Example 7.

The following thiazoline derivatives were prepared analogously to Example 5: 2 - (2 - ethyl - 4 - methyl - phenylimino) - 3 - methyl - thiazoline, boiling point: 149—152°C/1.0 mm Hg; 2 - (2 - methyl - 4 - tert. - butyl - phenylimino) - 3-methyl - thiazoline, boiling point: 169—173°C/1.1 mm Hg; 2 - (2,5 - dimethyl-4 - chloro - phenylimino) - 3 - methyl - thiazoline, boiling point: 168—170°C/1.0 mm Hg, solidified; 2 - (2,4 - dimethyl - 5 - chloro - phenylimino) - 3 - methyl-thiazoline, boiling point: 176—180°C/1.7 mm Hg.

The following N - aryl - N' - alkylthio ureas required as starting materials can be prepared according to Examples 1 and 3: N - (2 - ethyl - 4 - methyl-phenyl) - N' - methyl - thiourea, melting point: 126—128°C; N - (2 - methyl-4 - tert. - butyl - phenyl) - N' - methyl - thiourea, melting point: 166—167°C; N - (2,5 - dimethyl - 4 - chloro - phenyl) - N' - methyl - thiourea, melting point: 144—146°C; N - (2,4 - dimethyl - 5 - chloro - phenyl) - N' - methyl - thiourea, melting point: 173—174°C.

Example 8.

2-(2,6-diethyl-4-methyl-phenylimino)-3-methyl-thiazoline

40 g of N-(2,6-diethyl-4-methyl-phenyl)-N'-methyl-thiourea are stirred in 400 ml of acetone and 33 g of chloroacetaldehyde (45% aqueous solution) are added. The mixture is then refluxed for 2 hours and the solvent is distilled off. The residue is stirred with 300 ml of methylenechloride and with 300 ml of a 15 per cent solution of sodiumcarbonate, the methylenechloride phase is separated, washed with water, dried over potassium carbonate and distilled. 30 g of 2-(2,6-diethyl-4-methyl-phenylimino)-3-methyl-thiazoline are obtained (boiling point: 148—152°C, 1.0 Torr): elementary analysis, NMR and IR-spectra confirm the structure of the molecule.

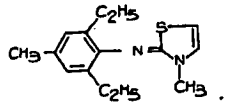
Example 9.

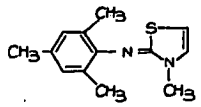
In an analogous manner to Example 8, from N - (2,4,6 - trimethyl - phenyl)-N'-methyl-thiourea the 2-(2,4,6-trimethyl-phenylimino)-3-methyl-thiazoline (oily substance, boiling point (1.0 Torr): 142—145°C) is obtained. The above used starting material N - (1,5 - diethyl - 4 - methyl - phenyl) - N' - methyl-thiourea may be synthesized in the following manner:

A mixture of 100 g of 4 - amino - 1 - methyl - 3,5 - diethyl - benzene 50 g of methyl - isothiocyanate and 150 g of triethylamine is kept for 24 hours at a temperature of 20°C. Then the mixture is stirred with diluted hydrochloric acid and the precipitated crystalline thiourea is filtered washed and dried. Yield: 133 g of the above thiourea, melting point: 100—102°C.

In an analogous manner, N - (2,4,6 - trimethyl - phenyl) - N' - methyl-thiourea having a melting point of 195—198°C and N - (2 - methyl - 6 - alkyl-phenyl) - N' - methyl - thiourea (melting point: 65—67°C) can be produced.

Efficacy of compounds according to Example 8 of the present application:

formula A: 

formula B: 

tested against the resistant Biarra strain of boophilus microplus in handspray by using a concentration of the active compound of 250 ppm. All states of development are given in vivo/cattle

Concentration of active compound 250 ppm	days before treatment −2 — +0	number of ticks with fertile eggs								Efficacy in %
		days after the treatment								
		+1–3	4–6	7–9	10–12	13–15	16–18	19–21	+1–21	
formula A	886	9	2	11	33	4	0	0	59	98.54
formula B	591	5	14	4	2	—	—	—	25	98
untreated control	903	1009	571	1025	679	710	706	839	5539	—

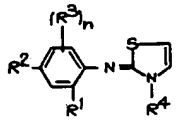
adults — nymphs — larvae

metanymphs — metalarvae

Approximate state of development at the time of treatment

WHAT WE CLAIM IS:—

1. A substituted 2-phenylimino-thiazoline of the formula (I)



(I)

in which

R^1 and R^2 can be identical or different and represent optionally substituted alkyl,

R^3 represents optionally substituted alkyl or halogen,

R^4 represents alkyl, cycloalkyl or alkenyl and

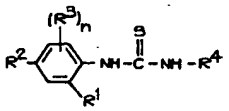
n represents 0, 1 or 2

or a salt thereof.

2. A compound according to claim 1 wherein R^1 and R^2 are identical or different and represent alkyl with 1 to 4 carbon atoms, R^3 represents alkyl with 1 to 4 carbon atoms or chlorine, R^4 represents alkyl with 1 to 4 carbon atoms or represents alkenyl with 2 to 4 carbon atoms and n represents 0, 1 or 2.

3. Any compound according to claim 1 specifically described herein, other than in Example 7.

4. A process for the preparation of a compound according to any one of claims 1 to 3 which comprises reacting a compound of the formula



(II)

in which

R^1, R^2, R^3, R^4 and n are as defined in claim 1, with a halogenoacetaldehyde or a compound which splits off a halogenoacetaldehyde and optionally converting the reaction products into a salt by means of an acid.

5. A process according to claim 4 wherein the reaction is carried out in the presence of a solvent and an acid-binding agent.

6. A process according to claim 4 or claim 5 wherein the reaction is carried out at a temperature of from 20 to 80°C.

7. A process for preparing a compound according to any one of claims 1 to 3 substantially as hereinbefore described in any one of Examples 1 to 6.

8. A compound according to claim 1 when prepared by a process according to any one of claims 4 to 7.

9. A formulation for use in the treatment of ectoparasites which comprises a compound according to any one of claims 1 to 3 and 8 in admixture with a solid or liquefied gaseous diluent or in admixture with a liquid diluent other than a solvent of molecular weight less than 200, except in the presence of a surface active agent.

10. A method of combating acarides which comprises applying to the acarides or a habitat thereof, a compound according to any one of claims 1 to 3 and 8 alone or in admixture with a diluent.

11. A method of combating ectoparasites on warm-blooded animals which comprises applying to the external surface of the animal a compound according to any one of claims 1 to 3 and 8 alone or in admixture with a diluent.

12. A compound according to claim 1 specifically described in any one of Examples 7 to 9.

13. A formulation according to claim 9 wherein the said compound is a compound according to claim 12.

14. A method according to claim 10 or claim 11 wherein the said compound is a compound according to claim 12.

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